| Table C-2. Adjuvant treatment for phenylketonuria (PKU) – LNAA evidence tables |
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| **Study Description** | **Intervention** | **Inclusion/ Exclusion Criteria/ Population** | **Baseline Measures** | **Outcomes** |
| Author: Matalon, 2007Country: Russia, Ukraine, US, Italy, Brazil, DenmarkEnrollment period: NRFunding: Genetics Research Trust, the Mid-Atlantic Connection for PKU and Allied Disorders (MACPAD), the South Texas Association for PKU and Allied Disorders (STAPAD), and PKU and Allied Disorders of Wisconsin (PADOW), PreKUNil and NeoPhe by PreKU lab, Denmark Author industry relationship disclosures: NoneDesign: RCT | **Intervention:** Double-blind placebo controlled crossover trial of tabletsof Large neutral Amino Acid (LNAA-NeoPhe) & placebo, with a random order of placebo & LNAA**Groups:** **G1:** LNAA / placebo **G2:** Placebo /LNAA**Dosage**: **G1:** 0.5 g/kg/day in 3 divided doses to be taken with meals, which is about one tablet/ kg/day.**G2:** same as G1 & contained lactose monohydrate, microcrystalline cellulose and colloidal hydrated silica.1 week washout period prior to the next week of crossover trialDiet was continued as before the trial**Assessments:** Blood Phe determined at the beginning & then twice weekly**Length of follow-up:** A week after treatment**Groups, N at enrollment:****G1/G2:** 20N at follow-up: **G1/G2:** 20 | Inclusion criteria: Should have PKU and old enough to swallow pills Exclusion criteria: See inclusion criteriaAge:G1/G2: range (11-32 years)Other characteristics, n:Disease classification: Classical PKU, 19  | **Cognitive:****IQ:**NR**Phe level, mean:****G1/G2:** 932.9 µmol/LThose adhered to PKU formula (n=7): 531.6 µmol /L**Nutritional:**NR**Quality of Life:**NR | **Cognitive:****IQ:**NR**Phe level, mean ± SD:** (µmol/L)**G1:** 568.4 (average decline of 364.5 ± 232.),39% reduction (*P* < 0.0001)**G1 and adhered to formula:** 281.5 (average decline of 250.1 ± 173.7), 47% reduction (*P* = 0.009)**G2**: 882.66 (decline of 5.4%) (*P* = 0.07)**Nutritional:**NR**Quality of Life:**NR**Harms:** NR**Modifiers:** NR |

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| Author: Schindeler, 2007Country: AustraliaEnrollment period: NRFunding: SHS InternationalAuthor industry relationship disclosures: NRDesign: RCTSchindeler, 2007 (continued)Schindeler, 2007 (continued) Schindeler, 2007 (continued) | **Intervention:** Double-blind, randomized crossover study with LNAA Dosage: 250mg/kg/day of LNAA, 3 equal daily doses 4 phases of study: **G1A:** Phase 1: Usual Medical product, usual Phe restricted diet & LNAA tablets**G1B:** Phase 2: Usual Medical product, usual Phe restricted diet & placebo tablets**G1C:** Phase 3: No Medical product, took usual Phe restricted diet & energy intake, LNAA tablets **G1D:** Phase 4: No Medical product, took usual Phe restricted diet & energy intake, Placebo tablets Duration: Each phase for 14 days with a 4 week washout period between phases**Assessments:** Brain Phe by MRSPlasma Phe at the completion of each phase 3 day food diary to assess intake of dietary protein Intelligence by WASI Components of attention & executive function by CPT-II, CANTAB, D-KEFS Self-report of mood ratings by DASSLength of follow-up: end of each phaseAll on diet & medical products for PKUAt the end of each phase: median (min,max), Phe intake mg/kg/day G1A: 18.6 (5.3, 27.9) G1B: 18.5 (6.4, 43.9) G1C: 17.5 (4.5, 29.7) G1D: 21.8 (6.2, 27.9)Protein total g/kg/day G1A: 1.62 (0.96, 2.10) G1B: 1.43 (0.88, 1.85) G1C: 0.63 (0.34,0.93) G1D: 0.51 (0.17,0.62)LNAA total g/kg/day G1A: 0.90 (0.53, 1.27) G1B: 0.75 (0.32, 1.05) G1C: 0.35 (0.24,0.46) G1D: 0.15 (0.05,0.21)Compliance on LNAA supplement - good**Groups, N at enrollment:****Total:** 16N at follow-up: **Total:** 16 | Inclusion criteria: Early treated Classical PKU (plasma Phe at some stage >1000 µmol/L) Currently on diet & medical products for PKUExclusion criteria: see inclusionAge, median/yrs: 24y 9 m, range (11y 8m to 45y 1m)Other characteristics, n (%): Classical PKU subjects=16 (100)  | **Cognitive:****IQ: mean (SD)**101 (16)**Phe level:** Previous year Median blood Phe levels used as baseline Excellent control (<450 µmol/L), n=0Good control (450-750 µmol/L), n=9Marginal control (750-1000 µmol/L), n=6Poor control (>1000 µmol/L), n=1**Nutritional:**NR**Quality of Life:**NR | **Cognitive:****IQ:** G1C vs. G1D:Better performance on measures of verbal generativity (*t*=2.657,*P =* 0.018) and non verbal cognitive flexibility (*t=*2.66, *P* = .018) G1C vs. G1A:Better verbal self monitoring (*t=*2.179, *p=*0.046) G1A & G1B vs. G1C & G1D:better performances onattention measures (*F=*23.64, *p=*0.000)**Phe level:**Brain Phe, µmol/L, range: 176-365 (no significant differences between phases)Plasma Phe µmol/L, at the end of each phase, median (min,max):G1A: 639 (149, 1044) G1B: 734 (19, 1231) G1C:958 (553, 1500) G1D: 1180 (641, 1744)Significant differences in plasma Phebetween G1C & G1D (p=0.001), between G1A & and G1C(*P* = 0.001), between G1A & G1D (*P* < 0.0005), betweenG1B and G1D (p=0.001), and between G1B and G1C (p=0.023). There was no significant difference between G1A and G1B (p=0.22), however, plasma Phe was reducedin most subjects (9 of 16) by an average of 24.9% during G1A**Plasma Phe/Tyr ratio:** median (min,max) ;G1A: 10 (1.2, 17.9) G1B:14 (0.2, 27.5) G1C:18 (8.6, 36.6) G1D: 30 (11.9, 52.1)**Plasma Phe/Tyr ratio:** significant differences between G1Aand G1B (*p=*0.017), between phase G1C and G1D (*p=*0.001), betweenG1A and G1C (*p=*0.02), between G1A and G1D (*p*<0.001),and between G1B and G1D (*p*<0.001) No significant diff between G1B & G1C (p=.23)**Nutritional:**G1A:NRG1B:NR G1C: NR G1D: NR**Quality of Life:**G1A:NRG1B:NR G1C: NR G1D: NR**Harms:** Higher levels of anxiety symptoms while on LNAA (F=5.2, p=.039), G1A & G1C compared to G1B & G1D**Modifiers:** No correlation between Plasma & brain Phe when Plasma Phe <1200 µmol/LG1D: Significant correlation between plasma & brain phe (r=0.90, p=.04, where phe ≥1200 µmol/L n=5) No significant correlationsBetween plasma Phe or Phe/Tyr ratio with total dietary LNAA intake, or dietary PheintakeG1A: significantnegative correlations were obtained between plasmaPhe and semantic verbal Fluency (VF-Category; r=- 0.525, p*=*0.018.G1B: plasma Phe and inattention Negatively correlated (CPT-Errors, r = - 0.441, *p=*.044). G1C: a negative correlation between spatialworking memory and plasma Phe (SWM,r= - 0.464, *p=*0.035). G1D: no significant correlations**Across phases,** Statistically significantnegative correlations between plasma Pheand verbal generativity (VF-Letters; r= - 0.465, (*p=*0.035)and non-verbal self monitoring (DF-reps, r = -0.488,*p=*0.027). |

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| Author: Matalon, 2006Country: US, Ukraine, RussiaEnrollment period: NRFunding: Genetics Research Trust Author industry relationship disclosures: NoneDesign: Uncontrolled open label trial | **Intervention:** Open-label study of LNAAs (NeoPhe)**Groups :** **G1:** 0.5g/kg/day of NeoPhe **G2:** 1.0 g/kg/day of NeoPheDuration: 1 weekFormulation: NeoPhe divided into 3 doses and taken before mealsInstructed to continue with their diet as before the trial**Assessments:** Blood Phe at baseline, 1 wk and 1 week after Rx **Length of follow-up:** 1 week after the end of Rx**Groups, N at enrollment:****G1:** 8**G2:** 3N at follow-up: **G1:** 8**G2:** 3 | Inclusion criteria:* Should have PKU
* Old enough to swallow pills

Exclusion criteria: See inclusion criteriaAge, mean/yrs : G1: 20.5 G2: 16.5**Other characteristics:** **G1+G2:** All 11 patients were classical PKU2 responded to BH4 loading, none were on BH4 during study | **Cognitive:****IQ:**NR**Phe level, mean****µmol/L:****G1:** 957.4 **G2:** 1,230**Nutritional:**NR**Quality of Life:**NR | **Cognitive:****IQ:**NR**Phe level, mean µmol/L ± SD:** **G1:** 458.4 **G2:** 549 Drop in Phe, mean ± SD: 601 + 370, n=11, (P = 0.0003)**% decline in Phe:****G1:** 52**G2:** 55 **G1/BL:** *P* = .004**Nutritional:**NR**Quality of Life:**NR**Harms:** NR**Modifiers:**NR |